Remarks

Claims 56-88 are pending. By this amendment, claims 73 and 75 have been amended. No new matter has been added.

Rejection under 35 USC 112, Second Paragraph

In the above-cited office action, various claims were rejected as allegedly being indefinite for using terms said to be functional, such as "reacting", "deprotecting", "coupling", "separating", "forming", "annealing", "extending" and "covalently attached".

In particular, the rejection indicated that (1) the claims should recite "how one of ordinary skill in the art would perform" the cited steps, (2) the claims must recite "reagents, the reaction times, pH, and reaction conditions that are applicable in the steps", (3) "Applicant may not claim all applicable processes of [the cited steps]" but must "claim only the processes of performing [those steps] that embody applicant's invention", (4) "...a process claim must recite 'how' the process is performed not 'what' is done," (5) "[a] claim must stand alone to define the inventions, and incorporation into the claims by reference to the specification or an external source is not permitted (citing Ex parte Fressola, 27 USPQ2d 1608, BPAI 1993), (6) "it is essential for claims to be precise, clear, correct, and unambiguous (citing In re Zietz, 13 USPQ2d 1320, Fed. Cir. 1989), and (7) the term "comprises" in claims 73 and 75 render the claims indefinite. These rejections are respectfully traversed.

The test for definiteness is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081, 1088 (Fed. Cir. 1988); MPEP §2173.02. The present claims meet that test.

Claim 1 recites a method of forming a labelled substrate comprising reacting a substrate with the linking moiety of a substantially pure atropisomer compound having the structure shown in claim 1, whereby a labelled substrate is formed.

Claim 64 recites a method of synthesizing a labelled polynucleotide comprising coupling a phosphoramidite compound of the structure shown in claim 46, which contains a substantially pure atropisomer of a captioned xanthene compound, to a polynucleotide, wherein the polynucleotide is bound to a solid support, whereby a labelled polynucleotide is formed.

Claim 65 recites a method of separating atropisomers of a C-11 aminomethyl, C-19 carboxyl fluorescein compound comprising: (a) reacting a C-11 aminomethyl, C-19 carboxyl fluorescein with a substantially pure enantiomer of an active ester or carboxylic acid to form diastereomeric carbamates; (b) separating the diastereomeric carbamates; and (c) hydrolyzing the separated diastereomers with aqueous acid.

Claims 68 and 70 recite methods of separating a mixture of labelled substrates comprising: (a) separating a mixture of labelled substrates by electrophoresis or chromatography; and (b) detecting the labelled substrates by fluorescence detection, wherein the labelled substrates are comprised of a substantially pure atropisomer of a xanthene compound having the structure shown in claim 68 or claim 70.

Claim 71 recites a method of generating a labelled primer extension product, comprising the step of extending a primer-target hybrid with an enzymatically-incorporatable nucleotide, wherein said primer or said nucleotide is labelled with a substantially pure atropisomer of a xanthene compound having the recited structure, whereby the rpimer is extended.

Claims 73 and 75 recite additional features of parent claim 71.

Claim 78 recites a method of polynucleotide sequencing comprising: a) forming a mixture of a first, a second, a third, and a fourth class of polynucleotides, such that: each polynucleotide in the first class includes a 3'-terminal dideoxyadenosine and is labelled with a first dye; each polynucleotide in the second class includes a 3'-terminal dideoxycytidine and is labelled with a second dye; each polynucleotide in the third class includes a 3'-terminal dideoxyguanosine and is labelled with a third dye; and each polynucleotide in the fourth class includes a 3'-terminal dideoxythymidine and is labelled with a fourth dye; wherein at least one of the first, second, third, or fourth dyes is a substantially pure atropisomer of a xanthene compound having the recited structure, and b) separating the polynucleotides on the basis of size.

Claim 81 recites a method of oligonucleotide ligation comprising annealing two probes to a target sequence ... wherein one or both probes are labeled with a substantially pure atropisomer of a xanthene compound having the recitd structure.

Claim 82 recites a method of fragment analysis fragment analysis comprising: separating labelled polynucleotide fragments by a size-dependent separation process; and detecting the separated labelled polynucleotide fragments subsequent to the separation process, wherein the fragments are labelled with a substantially pure atropisomer of a xanthene compound having the recited structure.

Claims 86, 87 and 88 recite methods of amplification involving primer annealing and extending steps, wherein at least one of the primers (or probe in claim 88) is a labelled polynucleotide comprising a polynucleotide covalently attached to a label, wherein the label is a substantially pure atropisomer of a xanthene compound having the recited structures.

(1) First, there is no requirement under 35 USC 112, second paragraph, that the claims recite "how one of ordinary skill in the art would perform" the cited steps. Rather, "those skilled in the art would understand [the metes and bounds] what is claimed when the claim is read in light of the specification." (*Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, cited above). In the present case, ample guidance can be found in the specification and references cited therein, such as, for example, at pages 12-16 (structure and synthesis of atropisomer compounds), page 16 line 16 to page 18 line 2 (resolution/separation of atropisomers), page 21 line 7 to page 32 line 26 (covalent attachment methods), and methods (page 32 et seq) such as methods comprising primer extension (pages 33-34), ligation (pages 34-35), amplification (pages 35-36), hybridization assays (page 36), chromatography (pages 36-37), sequencing methods, and the Examples on pages 37-48. For example, Examples 18 to 20 demonstrate illustrative sequencing methods using labeled terminators in accordance with the present invention, including illustrative annealing conditions. The skilled person would have no doubt about the metes and bounds of what is claimed.

(2) Second, there is no requirement to recite "reagents, the reaction times, pH, and reaction conditions that are applicable in the steps". Rather, method claims that recite one or more steps in a clear manner (when read in light of the teachings of the specification) meet the requirements of Section 112, second paragraph.

(3) Third, the claims indeed "claim only the processes of performing [those steps] that embody applicant's invention". The inventors do not assert that they invented each individual step. Rather, they invented methods that comprise one or more steps in relation to certain atropisomers.

(4) Fourth, by reciting specified steps, all of the claims recite "how" the claimed methods (processes) are performed.

(5) Fifth, Ex parte Fressola (27 USPQ2d 1608, BPAI, 1993) is not relevant to the present case. In the Fressola case, the claim was to "A system for the display of sterographic three-dimensional images of celestial objects as disclosed in the specification and drawings herein." Such wording (see underlining) does not appear in the present claims.

(6) Sixth, in the Zietz case (In re Zietz, 13 USPQ2d 1320, Fed. Cir. 1989), the Federal Circuit held that "it was incorrect for the Board to read unwritten limitations into [certain claims], contrary to the plain words of the claims, and contrary to the interpretation that the inventor himself placed on the claims" (Id, paragraph bridging columns 1 and 2 of page 1322). That issue is not present here. Although Zietz contains a passing statement that "An essential purpose of patent examination is to fashion claims that are precise, clear, correct, and unambiguous (Id, page 1322, column 1), the Applicant and the Examiner should be in agreement, since the present claims meet this standard.

(7) Finally, Applicant submits that the rejection of claims 73 and 75 is moot in light of amendment of these claims to replace "comprising" with "having", and "comprises" with "is", as suggested by the Examiner.

The applicants submit that the application is in condition for allowance. Early notice of allowance is respectfully requested.

FEE AUTHORIZATION and REQUEST FOR TIME EXTENSION

If any additional time extensions are required, such time extensions are hereby requested. If any additional fees not submitted with this response are required, please take such fees from Applied Biosystems Deposit Account No. **01-2213 (Order No. 4601D2)**.

Respectfully submitted,

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